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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Russia, PA 19406-0939 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: WEINSTOCK, Joseph [US/US]; 1234 Porthouse Road, Phoenixville, PA 19460 (US).

(74) Agents: McCARTHY, Mary, E. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

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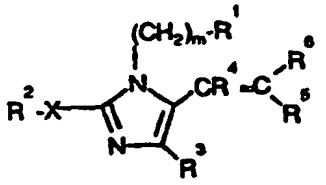

(I)

(57) Abstract

Angiotensin II receptor antagonists having formula (I) which are useful in regulating hypertension and in the treatment of congestive heart failure, renal failure, and glaucoma, pharmaceutical compositions including these antagonists, and methods of using these compounds to produce angiotensin II receptor antagonism in mammals.

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IMIDAZOLYL-ALKENOIC ACID ANGIOTENSIN II RECEPTOR ANTAGONISTS

The present invention relates to new imidazolyl-alkenoic acids which are angiotensin II receptor antagonists and are useful in regulating hypertension induced or exacerbated by angiotensin II, and in the treatment of congestive heart failure, renal failure, and glaucoma. This invention also relates to pharmaceutical compositions containing these compounds and methods for using these compounds as antagonists of angiotensin II, as antihypertensive agents and as agents for treating congestive heart failure, renal failure, and glaucoma.

BACKGROUND OF THE INVENTION

The class of peptide pressor hormone known as angiotensin is responsible for a vasopressor action that is implicated in the etiology of hypertension in man. Inappropriate activity of the renin-angiotensin systems appears to be a key element in essential hypertension, congestive heart failure and in some forms of renal disease. In addition to a direct action on arteries and arterioles, angiotensin II (AII), being one of the most potent endogenous vasoconstrictors known, exerts stimulation on the release of aldosterone from the adrenal cortex. Therefore, the renin-angiotensin system, by virtue of its participation in the control of renal sodium handling, plays an important role in cardiovascular hemeostasis.

Interruption of the renin-angiotensin system with converting enzyme inhibitors, such as captopril, has proved to be clinically useful in the treatment of hypertension and congestive heart failure (Abrams, W.B., et al., (1984), Federation Proc., 43, 1314). The most direct approach towards inhibition of the renin-angiotensin system would block the action of AII at the receptor. Compelling evidence suggests that AII also contributes to renal vasoconstriction and sodium retention that is characteristic of a number of disorders such as heart failure, cirrhosis and complications of pregnancy (Hollenberg, N.K., (1984), J. Cardiovas. Pharmacol., 6, S176). In addition, recent animal studies suggest that inhibition of the renin-angiotensin system may be beneficial in halting or slowing the progression of chronic renal failure (Anderson, S., et al., (1985), J. Clin. Invest., 76, 612). Also, a recent patent application (South African Patent Application No. 87/01,653) claims that AII antagonists are useful as agents for reducing and controlling elevated intraocular pressure, especially glaucoma, in mammals.

The compounds of this invention inhibit, block and antagonize the action of the hormone AII, and are therefore useful in regulating and moderating angiotensin induced hypertension, congestive heart failure, renal failure and other disorders attributed to the actions of AII. When compounds of this invention are

administered to mammals, the elevated blood pressure due to AII is reduced and other manifestations based on AII intercession are minimized and controlled. Compounds of this invention are also expected to exhibit diuretic activity.

Recognition of the importance of blocking and inhibiting the actions of AII has stimulated other efforts to synthesize antagonists of AII. The following references have disclosed imidazole derivatives which are described as having AII blocking activity and useful as hypotensive agents.

Furukawa et al., U.S. Patent 4,340,598 discloses imidazol-5-yl-acetic acids and imidazol-5-yl-propanoic acids. Specifically, the discloser includes 1-benzyl-2-n-butyl-5-chloroimidazole-4-acetic acid and 1-benzyl-2-phenyl-5-chloroimidazole-4-propanoic acid.

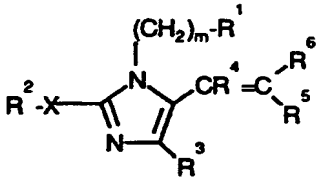
Furukawa, et al., U.S. Patent 4,355,040 discloses substituted imidazole-5-acetic acid derivatives. A compound specifically disclosed is 1-(2-chlorobenzyl)-2-n-butyl-4-chloroimidazole-5-acetic acid.

Carini et al. in EP 253,310 disclose certain imidazolylpropenoic acids. Two intermediates described in this patent are ethyl 3-[1-(4-nitrobenzyl)-2-butyl-4-chloroimidazol-5-yl]propenoate and ethyl 3-[2-butyl-4-chloro-1-(4-aminobenzyl)imidazol-5-yl]propenoate.

Also, Wareing, in PCT/EP 86/00297, discloses as intermediates certain imidazolylpropenoate compounds. On page 62, Formula (CX) is ethyl 3-[1(-4-fluorophenyl)-4-isopropyl-2-phenyl-1H-imidazol-5-yl]-2-propenoate.

DESCRIPTION OF THE INVENTION

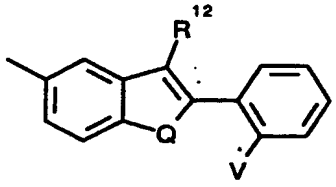
The compounds of the present invention that are blockers of angiotensin II receptors are represented by the following Formula (I):



(I)

in which:

R^1 is



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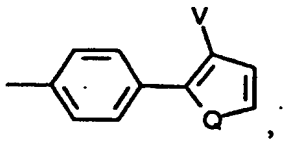

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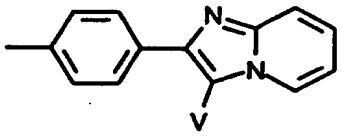

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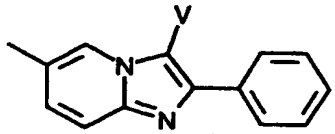

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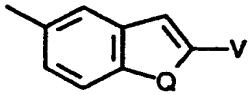

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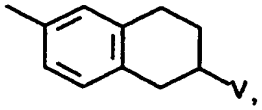

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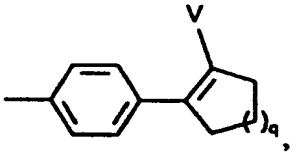

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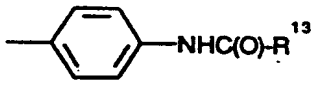

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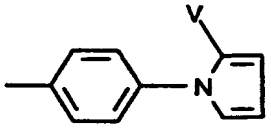

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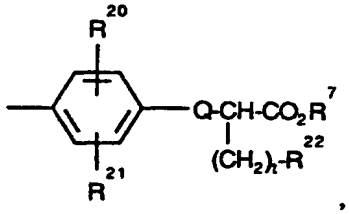

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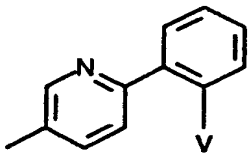

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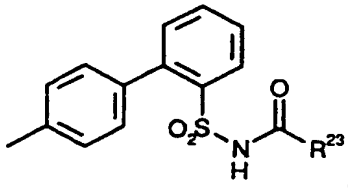

, or

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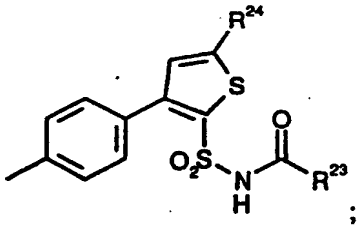


(13)

m is 0-4;

R^2 is C_2-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl, $(CH_2)_{0-8}$-C_3-C_6cycloalkyl, or $(CH_2)_{0-8}$phenyl unsubstituted or substituted by one to three substituents selected from C_1-C_6alkyl, nitro, Cl, Br, F, I, hydroxy, C_1-C_6alkoxy, NR^7R^7, CO_2R^7, CN, $CONR^7R^7$, W, tetrazol-5-yl, NR^7COC_1-C_6alkyl, NR^7COW, SC_1-C_6alkyl, SO_2W, or SO_2C_1-C_6alkyl;

X is a single bond, S, NR^7, or O;

R^3 is hydrogen, Cl, Br, F, I, CHO, hydroxymethyl, $COOR^7$, $CONR^7R^7$, NO_2, W, CN, NR^7R^7, phenyl, C_1-C_6alkyl, or $(CH_2)_{0-4}$-C_3-C_6cycloalkyl;

R^4 and R^5 independently are hydrogen, C_1-C_6alkyl, phenyl-Y-, biphenyl-Y-, naphthyl-Y-, 2- or 3-thienyl-Y-, 2- or 3-furanyl-Y-, 2-, 3- or 4-pyridyl-Y-, pyrazolyl-Y-, imidazolyl-Y-, pyrrolyl-Y-, triazolyl-Y-, oxazolyl-Y-, isoxazolyl-Y-, thiazolyl-Y-, or tetrazolyl-Y-, except that R^4 and R^5 are not selected from hydrogen and C_{1-6}alkyl, and with each heteroaryl group being unsubstituted or substituted by C_1-C_6alkyl, C_1-C_6alkoxy, Cl, Br, F, I, CF_3, NR^7R^7, CO_2R^7, SO_2NHR^7, SO_3H, $CONR^7R^7$, OH, NO_2, SC_1-C_6alkyl, SO_2C_1-C_6alkyl, NR^7COH, or NR^7COC_1-C_6alkyl and with each aryl group being unsubstituted or substituted by one to three substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, Cl, Br, F, I, CF_3, NR^7R^7, CO_2R^7, SO_2NHR^7, SO_3H, $CONR^7R^7$, OH, NO_2, SC_1-C_6alkyl, SO_2C_1-C_6alkyl, NR^7COH, or NR^7COC_1-C_6alkyl or with each aryl group being substituted by methylenedioxy, phenoxy, or phenyl;

Y is a single bond, O, S, or C_1-C_6alkyl which is straight or branched or optionally substituted by phenyl or benzyl, wherein each of the aryl groups is unsubstituted or substituted by halo, NO_2, CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, CN, or CO_2R^7;

R^6 is -Z-$COOR^8$ or -Z-$CONR^7R^7$;

Z is a single bond, vinyl, -CH_2-O-CH_2-, methylene optionally substituted by C_1-C_6alkyl, one or two benzyl groups, thienylmethyl, or furylmethyl, or -C(O)$NHCHR^9$-, wherein R^9 is H, C_1-C_6alkyl, phenyl, benzyl, thienylmethyl, or

furylmethyl;

W is C_nF_{2n+1};

each R^7 independently is hydrogen, C_1-C_6alkyl, or $(CH_2)_p$phenyl;

each n independently is 1-3;

each p independently is 0-4;

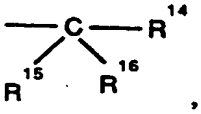
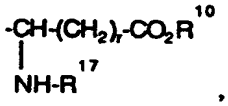
R^8 is hydrogen, C_1-C_6alkyl, or 2-di(C_1-C_6alkyl)-amino-2-oxoethyl;

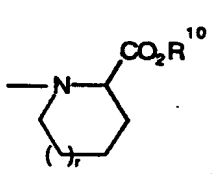
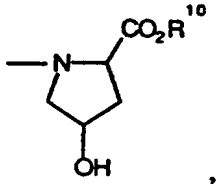
each R^{10} independently is H or C_1-C_6alkyl;

R^{11} is H, C_{1-6}alkyl, C_nF_{2n+1}, or -$(CH)_{0-2}$phenyl which is unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I, C_1-C_6alkyl, NO_2, CF_3, CO_2R^{10}, tetrazolyl, C_1-C_6alkoxy, OH, SC_1-C_6alkyl, SO_2NHR^{10}, $NHSO_2R^{10}$, SO_3H, $CONR^{10}R^{10}$, CN, SO_2C_1-C_6alkyl, $NR^{10}R^{10}$, $NR^{10}COH$, $NR^{10}COC_1$-C_6alkyl, or $NR^{10}CO$-phenyl;

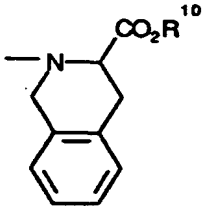
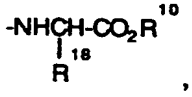
R^{12} is H, Br, Cl, F, I, CF_3, C_{1-4}alkyl, or C_1-C_4alkoxy;

R^{13} is

$-CH(R^{18})-NHR^{17}$,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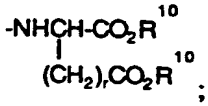
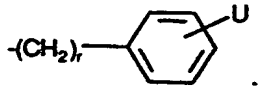

;

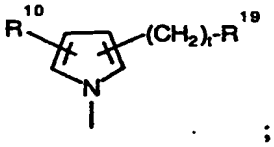
R^{14} is H, C_1-C_4alkyl, or


;

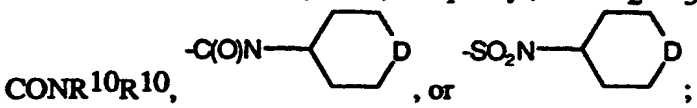
U is absent or present as Cl, Br, F, I, C_1-C_6alkyl, C_1-C_6alkoxy, or hydroxy;

R^{15} is hydrogen;

R^{16} is CN, CO_2H, tetrazolyl, or

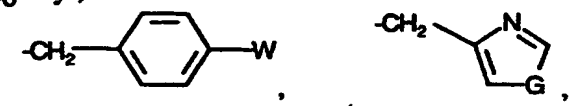


each R^{17} is CBZ, BOC, CO-phenyl, $COCH_2CH_3$, $COCH_3$, $COCF_3$,



;

R^{18} is H, C_{1-6}alkyl,



$-(CH_2)_3-NHC(=N)NH_2$, or $-(CH_2)_{3-4}NH_2$;

R^{19} is H, C_1-C_6alkyl, phenyl, CN, COR^{10}, CO_2R^{10}, tetrazolyl or

;

R^{20} and R^{21} independently are H, C_1-C_6alkyl, Cl, Br, F, I, C_1-C_6alkoxy, or phenyl, or when R^{20} and R^{21} are on adjacent carbon atoms, they are joined to form a phenyl ring;

R^{22} is $(CH_2)_{0-2}$phenyl unsubstituted or substituted by one to five substituents selected from Cl, Br, I, F, C_1-C_6alkyl, C_{1-5}alkoxy, C_{1-5}alkylthio, NO_2, CF_3, CO_2R^7, or OH;

each R^{23} independently is $-OCH_2$-phenyl unsubstituted or substituted by NHR^{25} or OR^{26};

R^{24} is C_1-C_4alkyl or C_3-C_6cycloalkyl;

R^{25} is H, C_1-C_4alkyl, C_3-C_6cycloalkyl or phenyl;

R^{26} is C_1-C_4alkyl or C_3-C_6cycloalkyl;

each Q independently is -O-, -S-, or $-N(R^{10})-$;

V is CO_2R^{10}, tetrazolyl, or $-NHSO_2R^{11}$;

q is 1-3;

each r independently is 0-3;

each t independently is 0-2;

A is CH or N;

D is $-CH_2-$, -O-, or $-N(R^{10})-$;

W is absent or present as OH or OC_{1-6}alkyl; and

G is -O-, -S-, or -NH-;

or a pharmaceutically acceptable salt thereof.

Preferably, one of R^4 and R^5 is hydrogen or C_1-C_6alkyl and m is one.

Preferred compounds of this invention are represented by Formula (I) when:

X is a single bond;

R^2 is C_2-C_8alkyl;

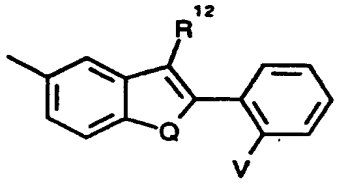
R^3 is hydrogen, chloro, fluoro, trifluoromethyl, C_1-C_6alkyl, or C_3-C_6cycloalkyl;

R^4 is hydrogen or C_1-C_6alkyl;

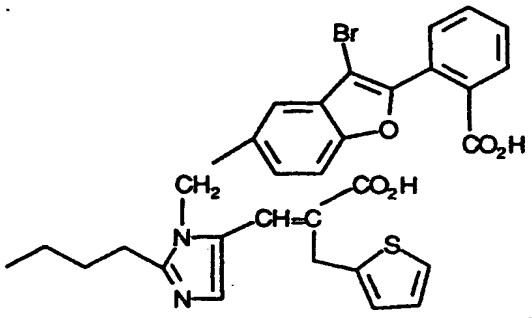
R^5 is thienylmethyl, furylmethyl, or imidazolylmethyl, each of which is optionally substituted by methyl or methoxy; and

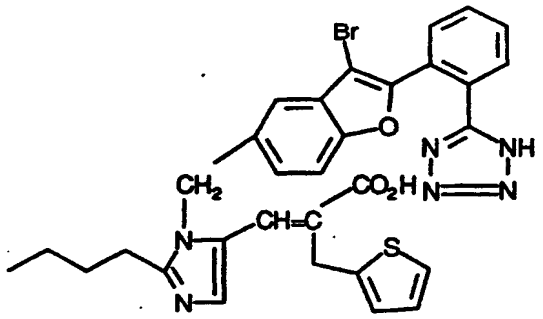
R^6 is COOH, $COOC_{1-2}$alkyl, or $CONH_2$; or a pharmaceutically acceptable salt thereof.

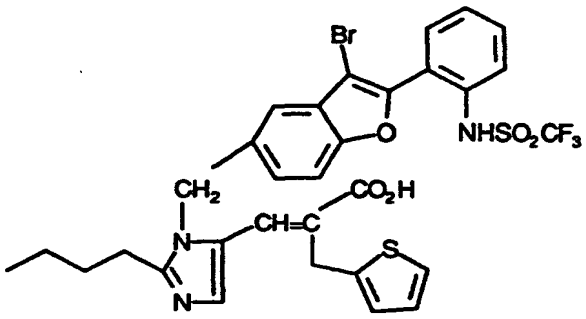
The most preferred compounds of this invention are represented by Formula (I) when R^1 is



Particular compounds of the invention include, but are not limited to, the following:







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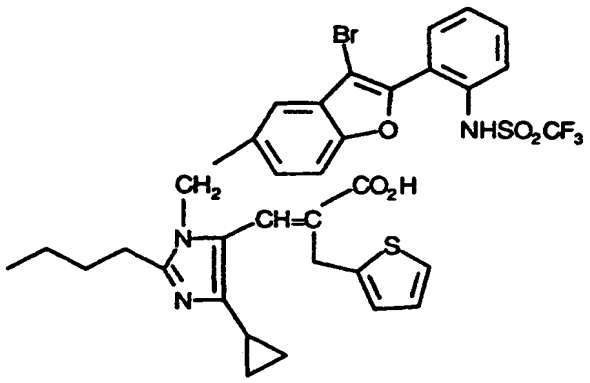

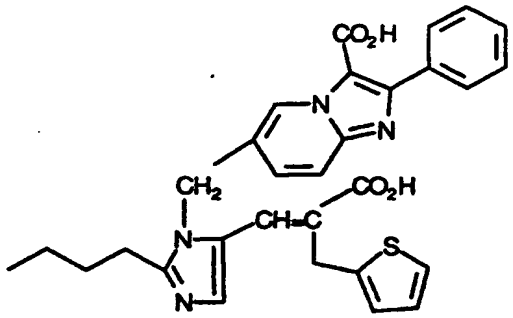

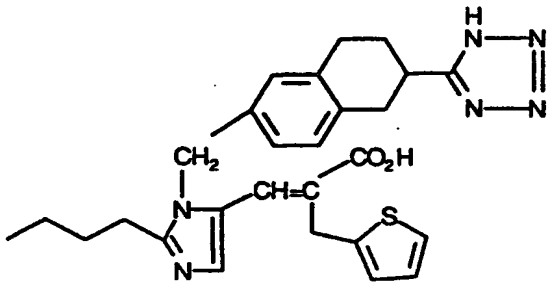

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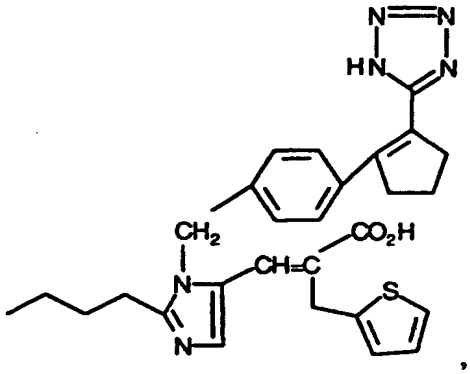

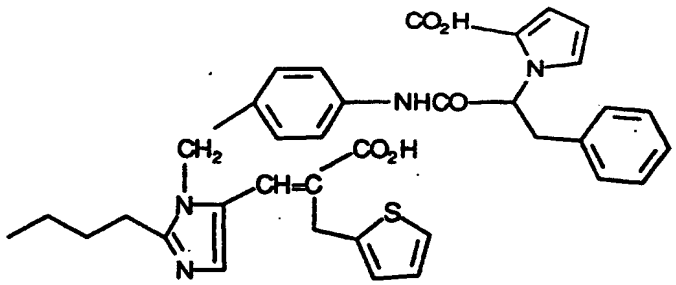

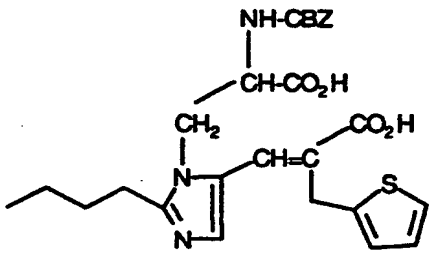

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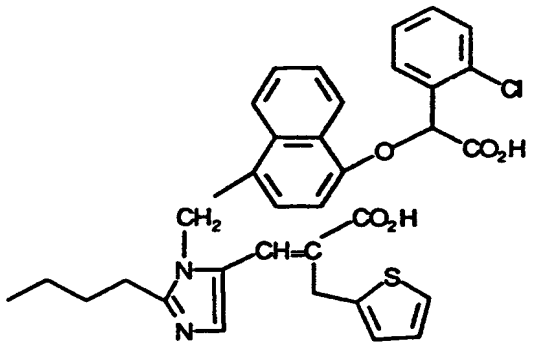

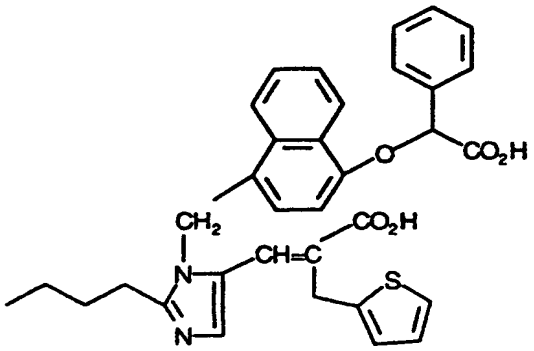

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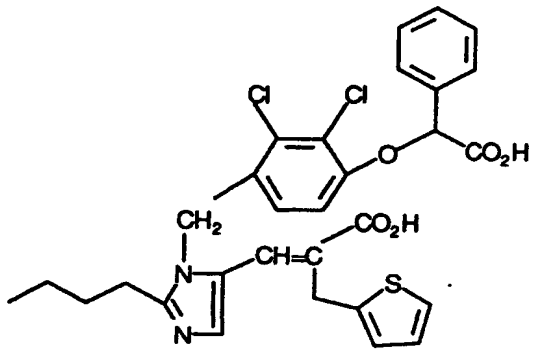

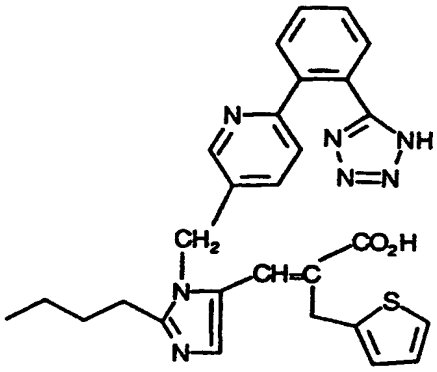

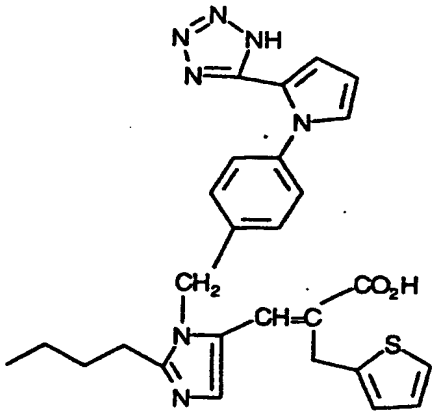

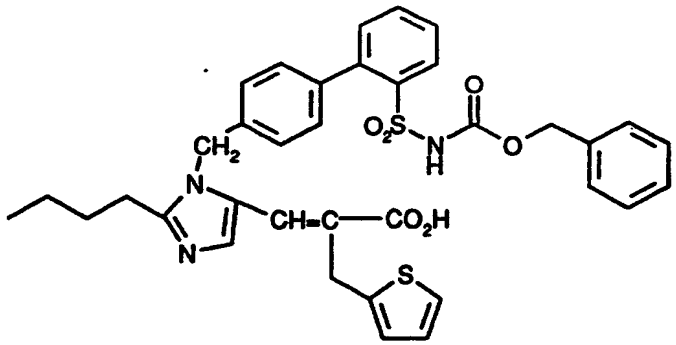

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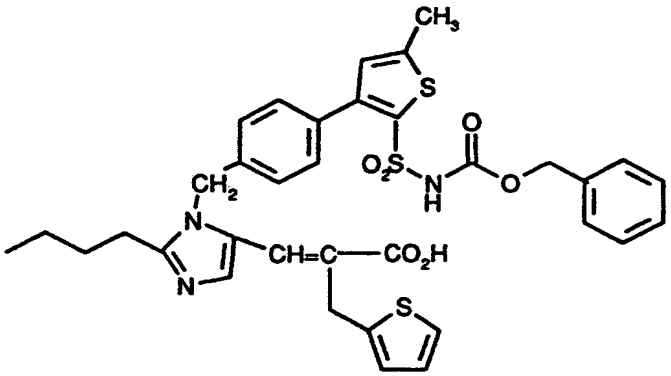
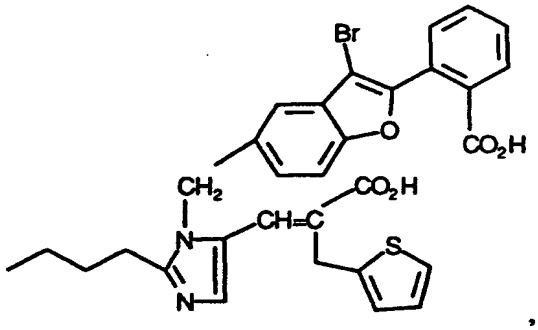


;

or pharmaceutically acceptable salts thereof.

The most preferred compounds of this invention are:



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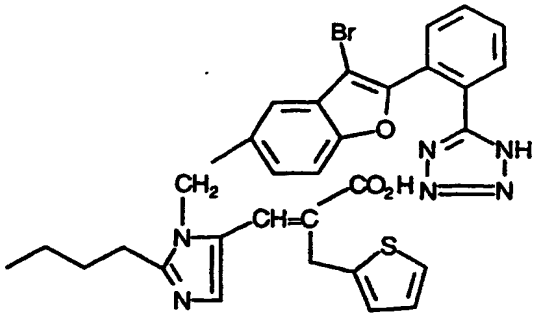

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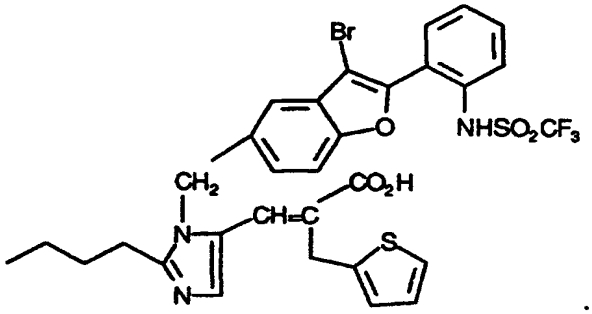


;

or pharmaceutically acceptable salts thereof.

The E isomers (trans stereochemistry of the R^6 group and imidazole group) are generally more active and, thus, are preferred over the Z isomers (cis).

As used herein, the terms alkyl, alkenyl, alkoxy and alkynyl mean carbon chains which are branched or unbranched with the length of the chain determined by the descriptor preceding the term.

Aryl, as used herein, means phenyl, biphenyl, or naphthyl. Heteroaryl means 2- or 3-thienyl, 2- or 3-furanyl, 2-, 3- or 4-pyridyl, pyrazolyl, imidazolyl, pyrrolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, or tetrazolyl.

Abbreviations commonly used in the peptide and chemical arts are used herein to describe certain compounds of this invention. For example, the abbreviation CBZ represents a benzyloxycarbonyl group and BOC represents a tert-butyloxycarbonyl group.

The invention also relates to pharmaceutical compositions comprising a pharmaceutical carrier and an effective amount of a compound of Formula (I).

Also included in the present invention are methods for antagonizing angiotensin II receptors which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I). Methods of treating hypertension, congestive heart failure, glaucoma, and renal failure by administering

these compounds are also included in this invention.

Because the compounds of Formula (I) are angiotension II receptor antagonists, they may also be of value in the treatment of left ventricular hypertrophy regression, diabetic nephropathy, diabetic retinopathy, macular degeneration, haemorrhagic stroke, angina, and anxiety. Additionally, these compounds may be expected to be useful in the primary and secondary prevention of infarction, in the prevention of atheroma progression and in the regression of antheroma, in the prevention of restinosis after angioplasty or bypass surgery and in the improvement of cognitive funtion.

The compounds of this invention are prepared by procedures described herein and illustrated by the examples. Reagents, protecting groups and functionality on the imidazole and other fragments of the molecule must be consistent with the proposed chemical transformations. Steps in the synthesis must be compatible with the functional groups and the protecting groups on the imidazole and other parts of the molecule.

The starting materials, 2-R^2X-imidazole, are known to the art (J. Org. Chem. 45:4038, 1980) or are synthesized by known procedures. For example, imidazole is converted to 2-n-butylimidazole by reacting imidazole with triethylorthoformate and p-toluenesulfonic acid to give 1-diethoxyorthoamide imidazole and then treating with n-butyl lithium to give the 2-lithium derivative of the orthoamide and alkylating with n-butyl iodide in a suitable solvent, such as tetrahydrofuran (THF).

The 1-$R^1(CH_2)_m$-group is incorporated onto the 2-R^2X-imidazole by known procedures, for example, by reaction with an R^1-$(CH_2)_m$ halide, mesylate or acetate, in a suitable solvent, such as dimethylformamide (DMF), in the presence of a suitable acid acceptor, such as sodium alkylate, potassium or sodium carbonate, or a metal hydride, preferably sodium hydride at a reaction temperature of about 25°C to about 100°C, preferably at about 50°C. The resulting 1-$R^1(CH_2)_m$-2-R^2X-imidazole is hydroxymethylated in the 5-position, for example, by reacting with formaldehyde in the presence of sodium acetate in acetic acid to provide the 1-R^1CH_2-2-R^2X-5-hydroxymethylimidazole intermediates.

Alternatively, the 1-$R^1(CH_2)_m$-2-R^2-5-hydroxymethyl-imidazole intermediates are prepared by reacting an imido ether, R^2-C(=NH)-O-alkyl, such as valeramidine methyl ether, with dihydroxyacetone in liquid ammonia under pressure to give 2-R^2-5-hydroxymethylimidazole. This intermediate is reacted with acetic anhydride to give 1-acetyl-5-acetoxymethyl-2-R^2-imidazole. The diacetate intermediate is N-alkylated and the resulting 1-$R^1(CH_2)_m$-2-R^2-5-acetoxy-

methylimidazole is treated with aqueous base, such as 10% sodium hydroxide solution, to give the 1-$R^1(CH_2)_m$-2-R^2-5-hydroxymethyl-imidazole intermediate.

Alternatively, the 2-R^2S-imidazole compounds are prepared by the following procedure. Benzylamines, substituted by one to three substituents selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, CN, NO_2, CF_3, CO_2C_{1-6}alkyl, SC_{1-6}alkyl, or SO_2C_{1-6}alkyl, are alkylated with a C_{1-6}alkyl chloroacetate, for example methyl chloroacetate, in the presence of a base, such as triethylamine, in a suitable solvent, such as dimethylformamide. The resulting alkylaminoalkyl ester compounds are N-formulated with formic acid in the presence of a suitable solvent, such as xylenes, followed by C-formulation of the carbon alpha to both the amino and the ester groups. Reaction of this intermediate with acidic thiocyanate, preferably potassium thiocyante, in an inert organic solvent, such as a C_{1-4}alkyl alcohol, produces 1-R^1CH_2-2-mercapto-5-alkanoate ester imidazole compounds. The free thio group of the ester imidazole is reacted with a halo-R' compound, wherein R' is C_{2-10}alkyl, C_{3-10}alkenyl, C_3-C_{10}alkynyl, C_3-C_6cycloalkyl or an optionally substituted $(CH_2)_{0-8}$phenyl, preferably propyl bromide, in the presence of a suitable base, such as sodium carbonate, in an appropriate solvent, such as ethyl acetate. The ester is reduced to the hydroxymethylimidazole intermediate by reduction with a suitable reagent, preferably diisobutyl aluminum hydride, in an appropriate solvent, such as tetrahydrofuran, at a temperature of about -78°C to about 25°C, preferably at less than -10°C.

The hydroxymethyl group of the hereinbefore prepared intermediate is oxidized to an aldehyde by treatment with a suitable reagent, such as anhydrous chromic acid-silica gel in tetrahydrofuran or, preferably, with activated manganese dioxide, in a suitable solvent, such as benzene or toluene, or preferably methylene chloride, at a temperature of about 25°C to about 140°C, preferably at about 25°C. The 1-$R^1(CH_2)_m$-2-R^2X-imidazol-5-carboxaldehydes are reacted with appropriate phosphonates, which are prepared, for example, from trialkyl phosphonoacetates by alkylation with an appropriate halide, mesylate or acetate in the presence of a suitable base, such as sodium hydride, in a suitable solvent, preferably glyme at a reaction temperature of about 25°C to about 110°C, preferably at about 55°C, to provide the appropriate phosphonates. The reaction of the imidazol-5-carboxaldehydes with the phosphonates is performed in the presence of a suitable base, such as a metal alkoxide, lithium hydride or preferably sodium hydride, in a suitable solvent, such as ethanol, methanol, ether, dioxane, tetrahydrofuran, or preferably glyme, at a reaction temperature of about 10°C to about 50°C, preferably at about 25°C, to provide a variable mixture of trans and cis, e.g., (E) and (Z), 1-

$R^1(CH_2)_m$-2-R^2X-5-CH=C(R^5)-(COOalkyl)-imidazoles. These isomers are readily separated by chromatography over silica gel in suitable solvent systems, preferably hexane in ethyl acetate mixtures. The esters are hydrolyzed to the acids, 1-R^1-$(CH_2)_m$-2-R^2X-5-CH=C(R^5)COOH-imidazoles, using bases, such as potassium hydroxide, lithium hydroxide or sodium hydroxide, in a suitable solvent system, such as, for example, aqueous alcohols or diglyme. The trans and cis structures of the acids are readily determined by NMR by the NOE protocol, as well as by the biological activities since, generally, the trans (E) isomeric acids are the more potent isomers.

Alternatively, the 1-$R^1(CH_2)_m$-2-R^2X-imidazol-5-carboxaldehydes are prepared by the following procedure. Starting 2-R^2X-imidazol-5-carboxaldehydes are reacted with an N-alkylating protecting reagent, such as chloromethyl pivalate (POM-Cl), in the presence of a base, such as potassium carbonate, in a suitable solvent, such as dimethylformamide, at a temperature of about 20°C to about 50°C, preferably at about 25°C, to give N-alkylation (e.g., POM-derivation) on the least hindered nitrogen atom of the imidazole nucleus. The 1-$R^1(CH_2)_m$-group is incorporated onto the imidazole by N-alkylation of the above prepared aldehyde with a halomethyl-substituted R^1 compound at a temperature of about 80°C to about 125°C, preferably at about 100°C. The protecting group on the 3-nitrogen of the imidazole ring is removed by base hydrolysis, for example using a biphasic mixture of ethyl acetate and aqueous sodium carbonate, to give 1-R^1CH_2-2-R^2X-imidazole-5-carboxaldehyde compounds. The Formula (I) compounds can be prepared from these 5-carboxaldehyde compounds by the methods described above.

Alternately, the 2-R^2X-imidazole starting materials are reacted with trimethylsilylethoxymethyl(SEM) chloride to give 1-(trimethylsilyl)ethoxymethyl-2-R^2X-imidazole. The reaction is carried out, for example, in the presence of sodium hydride in a solvent such as dimethylformamide. The 5-tributyltin derivatives are prepared by lithiation with, for example, butyllithium in a suitable solvent, preferably diethyl ether, followed by treatment of the lithio imidazole derivative with a tributyltin halide, preferably tri-n-butyltin chloride, at about -10°C to about 35°C, preferably at about 25°C. The 1-SEM-2-R^2X-5-tributyltinimidazole is coupled with an α,ß-unsaturated acid ester having a leaving group on the ß-position, such as a halide or trifluoromethanesulfonyloxy group, for example, BrCR^4=C(R^5)(COOalkyl), in the presence of a phosphine ligand, such as bis(diphenyl-phosphino)propane, or triphenylphosphine and a palladium (II) compound, or preferably tetrakis(triphenylphosphine)palladium(O), with or without a base, such as tributylamine, at a temperature of about 50°C to about 150°C,

preferably at about 120°C. Both the (E) and (Z) olefinic isomers are prepared by this procedure, and the isomeric esters are readily separated by chromatography over silica gel. The 1-SEM group from the (E) and (Z) isomers is hydrolyzed with acid, for example, aqueous hydrochloric, in a suitable alcoholic solvent, such as methanol or ethanol, and the 1-unsubstituted imidazole derivatives are converted to the 1-t-butoxycarbonyl (t-BOC) imidazoles with di-t-butyl dicarbonate (Hoppe-Seyler's Z. Physiol. Chem., (1976), 357, 1651). The t-BOC esters are hydrolyzed and N-alkylated to afford the 1-$R^1(CH_2)_m$-imidazole derivatives (esters). The (E) and (Z) isomers are hydrolyzed to the (E) and (Z) acids by the method described above.

Compounds of Formula (I) are also prepared by the following procedure. The 1-$R^1(CH_2)_m$-2-R^2X-imidazole-5-carboxaldehydes, prepared as described above, are reacted with a substituted half-acid, half-ester derivative of a malonate, such as ethyl 2-carboxy-3-(2-thienyl)propionate, in the presence of a base, such as piperidine, in a suitable solvent, such as toluene, at a temperature of about 80°C to about 110°C, preferably at about 100°C. The resulting 1-$R^1(CH_2)_m$-2-R^2X-5-CH=C(R^5)COOalkylimidazoles are hydrolyzed to the corresponding Formula (I) acid compounds by alkaline hydrolysis as described above.

Compounds of Formula (I) are also prepared as follows. The 1-R^1-$(CH_2)_m$-2-R^2X-imidazol-5-carboxaldehydes are treated with the lithium derivative of a substituted ethyl or methyl ester. These lithio derivatives are prepared from the reaction of lithium diisopropylamide in a suitable solvent, preferably tetrahydrofuran, with an acid ester, such as ROOC-CH_2-Y-(2-thienyl), to generate the α-lithio derivatives at about -78°C to about -10°C, preferably at about -78°C, which are then treated with the imidazol-carboxaldehyde. The intermediate ß-hydroxy group of the imidazole ester is converted to a mesylate or an acetate and the mesylate, or preferably the acetate, is heated in a suitable solvent, such as toluene, with one to two equivalents of 1,8-diazo-bicyclo[5.4.0]undec-7-ene, at about 50 to about 110°C, preferably at about 80°C, to afford ester compounds of Formula (I) such as 3-(imidazol-5-yl)-2-(2-thienyl)methyl-2-propenoic acid esters. The (E) isomer is the predominate olefinic isomer. The acids are prepared from the esters by the method described above.

Compounds of Formula (I) in which R^6 is Z-$COOR^8$ where Z is an optionally substituted methylene group are prepared by reducing the trans or (E) isomers of 3-(imidazol-5-yl)-2-propenoic acid esters (prepared as described above) with an appropriate hydride reagent, preferably diisobutylaluminum hydride, in a suitable solvent, such as tetrahydrofuran, to provide the unsaturated alcohol

compounds. These compounds are reacted with ethyl chloroformate, for example, with a base, preferably triethylamine, in a suitable solvent, such as tetrahydrofuran, to give 5-EtOOCOCH$_2$CR^5=CR^4-imidazoles which are reacted with carbon monoxide in the presence of a phosphine ligand, preferably triphenylphosphine with palladium (II) acetate, in a suitable solvent, preferably tetrahydrofuran, at a temperature of about 25°C to about 100°C, preferably at about 40°C, to give the 5-EtOOCCH$_2$CR^5=CR^4-imidazoles. The corresponding acids are prepared from these ethyl esters by base hydrolysis as described above.

Compounds of Formula (I) in which Z is -CH$_2$COOR^8 having additional substitution on the carbon a to the carboxylate group are prepared by converting 5-EtOOCH$_2$CR^5=CH^4-imidazoles to the lithium derivative of the ester with a lithium dialkylamide, preferably lithium diisopropylamide, and then treating with an alkylating agent, such as methyl halide, benzyl bromide, or heterocyclic methyl halide, to provide the mono-alkylated product compounds or the dialkylated product compounds. The acid compounds are prepared from the esters by base hydrolysis.

Compounds of Formula (I) in which R^6 is Z-COOR^8 where Z is -CH$_2$-O-CH$_2$- are prepared from unsaturated alcohol compounds, which had been obtained by the reduction of the Formula (I) propenoic acid esters. The alcohol is reacted with an appropriate hydride reagent, such as sodium hydride, in a suitable solvent, such as glyme, followed by reaction with an alkylating reagent, such as methyl bromoacetate, to give the 5-MeOOCCH$_2$-O-CH$_2$CR^5=CR^4-imidazoles. The corresponding acids are prepared from these esters by base hydrolysis as described above.

Compounds of Formula (I) in which R^6 is Z-COOR^8 where Z is -C(O)NHCHR^9- are prepared from the Formula (I) propenoic acid compounds. These acids are reacted with an appropriately substituted amino acid, such as glycine methyl ester hydrochloride or phenylalanine methyl ester hydrochloride, in the presence of an amide-forming reagent, such as N-hydroxysuccinimide and dicyclohexylcarbodiimide, in the presence of a base, for example triethylamine, in a suitable solvent, such as tetrahydrofuran, at a temperature of about 20°C to about 50°C, preferably at about 35°C. The 5-C$_{1-4}$alkyl-OOCCHR^{9}NHC(O)-CH$_2$CR^5=CR^4-imidazoles are converted to their corresponding acids by base hydrolysis as described above.

Formula (I) compounds which are substituted by hydroxy are formed from Formula (I) compounds which are substituted by C$_1$-C$_4$alkoxy using an ether-cleaving reagent, such as boron tribromide or hydrobromic acid.

Formula (I) compounds which are substituted by carboxy are formed from

Formula (I) compounds which are substituted by CO_2C_1-C_4alkyl using basic hydrolysis, such as aqueous sodium or potassium hydroxide in methanol or ethanol, or using acidic hydrolysis, such as aqueous hydrochloric acid.

Formula (I) compounds which are substituted by a tetrazol-5-yl group are prepared from the correponding carboxy compounds. For example, Formula (I) acid compounds are reacted with a halogenating agent, such as thionyl chloride, in a suitable solvent, for example benzene, to give the corresponding acid halide compounds. The acid halides are then converted to primary amide compounds, which are Formula (I) compounds that are substituted by $CONH_2$, in a reaction with concentrated ammonia. Subsequent dehydration of the amides with oxalyl chloride/dimethylformamide in acetonitrile/dimethylformamide yields the nitrile compounds, which are the immediate precursors to the Formula (I) tetrazole compounds. Tetrazole formation is accomplished by reacting the nitriles with azide, preferably aluminum azide prepared in situ by the reaction of sodium azide with aluminum chloride, in a suitable solvent, for example tetrahydrofuran. The Formula (I) compounds in which R^6 is -Z-CO_2H are prepared from these Formula (I) tetrazole ester compounds by basic hydrolysis as described above.

The various $R^1(CH_2)_m$-halides or alcohols useful in the preparation of Formula (I) compounds are known in the art or can be made by analogy processes using standard procedures of organic chemistry. The publications hereinbelow detail the preparation of the various $R^1(CH_2)_m$-halides or alcohols and the incorporation thereof onto an imidazole nucleus. Reference should be made to such publications for their disclosure, which are incorporated herein by reference.

Methods for preparing the halomethyl derivatives of the R^1 group of formula (1) and the incorporation thereof onto an imidazole nucleus are detailed in Middlemis, et al., Biorganic & Medicinal Chemistry Letters, 1(12):711 (1991).

Methods for preparing the halomethyl derivatives of the R^1 group of formula (2) and the incorporation thereof onto an imidazole nucleus are detailed in EP Publication No. 253 310.

Methods for preparing the halomethyl derivatives of the R^1 group of formula (3) and the incorporation thereof onto an imidazole nucleus are detailed in German Patent Application No. 4,023,215 and EP Publication No. 468 372.

Methods for preparing the halomethyl derivatives of the R^1 group of formula (4) and (5) and the incorporation thereof onto an imidazole nucleus are detailed in EP Publication No. 450 566.

Methods for preparing the halomethyl derivatives of the R^1 group of formula (6) and the incorporation thereof onto an imidazole nucleus are detailed in

Bühlmayer, et al., J. Med. Chem., 34:3105 (1991).

Methods for preparing the halomethyl derivatives of the R^1 group of formula (7) and the incorporation thereof onto an imidazole nucleus are detailed in Lin, et al., J. Med. Chem., 35:2658 (1992).

Methods for preparing the halomethyl derivatives of the R^1 group of formula (8) and the incorporation thereof onto an imidazole nucleus are detailed in PCT Publication No. WO 92/06081 and U.S. Patent No. 5,045,540.

Methods for preparing halomethyl derivatives of the R^1 group of formula (9) and the incorporation thereof onto an imidazole nucleus are detailed in EP Publication No. 480 204.

Methods for perparing halomethyl derivatives of the R^1 group of formula (10) and the incorporation thereof onto a fused imidazole core are detailed in PCT Publication No. WO 91/11999.

Methods for preparing halomethyl derivatives analogous to the R^1 group of formula (11) and the incorporation thereof onto an imidazole nucleus are detailed in EP Publication No. 480 204.

If the R^1-$(CH_2)_m$-mesylate or acetate is employed in the process of incorporating the R^1 $(CH_2)_m$-group onto the imidazole ring, then the mesylate or acetate is prepared from the corresponding alcohol in a reaction with methanesulfonyl chloride in pyridine or in a reaction with acetic anhydride and processes analogous to those detailed in the references hereinabove are employed to incorporate the $R^1(CH_2)_m$-group onto the imidazole ring.

It should be appreciated by those skilled in the art that the imidazole ring substituted by a $R^1(CH_2)_m$-group and a substituted acrylic acid group are prepared by processes analogous to those detailed in U.S. Patent No. 5,185,351. Reference should be made to such patent for its disclosure, which is incorporated herein by reference.

Pharmaceutically acceptable acid addition salts of compounds of Formula (I) are formed with appropriate organic or inorganic acids by methods known in the art. For example, the base is reacted with a suitable inorganic or organic acid in an aqueous miscible solvent such as ethanol with isolation of the salt by removing the solvent or in an aqueous immiscible solvent when the acid is soluble therein, such as ethyl ether or chloroform, with the desired salt separating directly or isolated by removing the solvent. Representative examples of suitable acids are maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic,

benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

Pharmaceutically acceptable base addition salts of compounds of Formula (I) in which R^8 is H are prepared by known methods from organic and inorganic bases, including nontoxic alkali metal and alkaline earth bases, for example, calcium, lithium, sodium, and potassium hydroxide; ammonium hydroxide, and nontoxic organic bases, such as triethylamine, butylamine, piperazine, meglumine, choline, diethanolamine, and tromethamine.

Angiotensin II antagonist activity of the compounds of Formula (I) is assessed by in vitro and in vivo methods. In vitro antagonist activity is determined by the ability of the compounds to compete with ^{125}I-angiotensin II for binding to vascular angiotensin II receptors and by their ability to antagonize the contractile response to angiotensin II in the isolated rabbit aorta. In vivo activity is evaluated by the efficacy of the compounds to inhibit the pressor response to exogenous angiotensin II in conscious rats and to lower blood pressure in a rat model of renin dependent hypertension.

Binding

The radioligand binding assay is a modification of a method previously described in detail (Gunther et al., Circ. Res. 47:278, 1980). A particular fraction from rat mesenteric arteries is incubated in Tris buffer with 80 pM of ^{125}I-angiotensin II with or without angiotensin II antagonists for 1 hour at 25°C. The incubation is terminated by rapid filtration and receptor bound ^{125}I-angiotensin II trapped on the filter is quantitated with a gamma counter. The potency of angiotensin II antagonists is expressed as the IC_{50} which is the concentration of antagonist needed to displace 50% of the total specifically bound angiotensin II.

Aorta

The ability of the compounds to antagonize angiotensin II induced vasoconstriction is examined in the rabbit aorta. Ring segments are cut from the rabbit thoracic aorta and suspended in organ baths containing physiological salt solution. The ring segments are mounted over metal supports and attached to force displacement transducers which are connected to a recorder. Cumulative concentration response curves to angiotensin II are performed in the absence of antagonist or following a 30-minute incubation with antagonist. Antagonist disassociation constants (K_B) are calculated by the dose ratio method using the mean effective concentrations.

Inhibition of pressor response to angiotensin II in conscious rats

Rats are prepared with indwelling femoral arterial and venous catheters and a stomach tube (Gellai et al., Kidney Int. 15:419, 1979). Two to three days following surgery the rats are placed in a restrainer and blood pressure is continuously monitored from the arterial catheter with a pressure transducer and recorded on a polygraph. The change in mean arterial pressure in response to intravenous injections of 250 mg/kg angiotensin II is compared at various time points prior to and following the administration of the compounds intravenously or orally at doses of 0.1 to 300 mg/kg. The dose of compound needed to produce 50% inhibition of the control response to angiotensin II (IC_{50}) is used to estimate the potency of the compounds.

Antihypertensive activity

The antihypertensive activity of the compounds is measured by their ability to reduce mean arterial pressure in conscious rats made renin-dependent hypertensive by ligation of the left renal artery (Cangiano et al., J. Pharmacol. Exp. Ther. 208:310, 1979). Renal artery ligated rats are prepared with indwelling catheters as described above. Seven to eight days following renal artery ligation, the time at which plasma renin levels are highest, the conscious rats are placed in restrainers and mean arterial pressure is continuously recorded prior to and following the administration of the compounds intravenously or orally. The dose of compound needed to reduce mean arterial pressure by 30 mm Hg (IC_{30}) is used as an estimate of potency.

The intraocular pressure lowering effects employed in this invention may be measured by the procedure described by Watkins, et al., J. Ocular Pharmacol., 1 (2):161-168 (1985).

The compounds of Formula (I) are incorporated into convenient dosage forms, such as injectable preparations, or for orally active compounds, capsules or tablets. Solid or liquid pharmaceutical carriers are employed. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid, such as an ampoule, or an aqueous or nonaqueous liquid suspension.

For topical ophthalmolgic administration, the pharmaceutical compositions adapted include solutions, suspensions, ointments, and solid inserts. Typical pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or vegetable oils, and water soluble ophthalmologically acceptable non-toxic polymers, for example, cellulose derivatives such as methyl cellulose. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting, and bodying agents, as for example, polyethylene glycols; antibacterial components, such as quarternary ammonium compounds; buffering ingredients, such as alkali metal chloride; antioxidants, such as sodium metabisulfite; and other conventional ingredients, such as sorbitan monolaurate.

Additionally, suitable ophthalmic vehicles may be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems.

The pharmaceutical preparation may also be in the form of a solid insert. For example, one may use a solid water soluble polymer as the carrier for the medicament. Solid water insoluble inserts, such as those prepared from ethylene vinyl acetate copolymer, may also be utilized.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral, parenteral, or topical products.

Doses of the compounds of Formula (I) in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity selected from the range of .01 - 200 mg/kg of active compound, preferably 1 - 100 mg/kg. The selected dose is administered to a human patient in need of angiotensin II receptor antagonism

from 1-6 times daily, orally, rectally, topically, by injection, or continuously by infusion. Oral dosage units for human administration preferably contain from 1 to 500 mg of active compound. Preferably, lower dosages are used for parenteral administration. Oral administration, at higher dosages, however, also can be used when safe and convenient for the patient. Topical formulations contain the active compound in an amount selected from 0.0001 to 0.1 (w/v%), preferably from 0.0001 to 0.01. As a topical dosage unit form, an amount of active compound from between 50 ng to 0.05 mg, preferably 50 ng to 5 mg, is applied to the human eye.

The compounds of this invention may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially. Conviently the compounds of this invention and the other active compound or compounds are formulated in a pharmaceutical composition. Examples of compounds which may be included in pharmaceutical compositions with the compounds of Formula (I) are diuretics, particularly a thiazide diuretic, such as hydrochlorothiazide, or a loop diuretic, such as furosemide, a calcium channel blocker, particularly dihydropyridine antagonists, such as nifedipine, ß-adrenoceptor blockers, such as propranolol, renin inhibitors, such as enalkinen, and angiotensin converting enzyme inhibitors, such as captopril or enalapril.

The AII receptor antagonist compounds of this invention can also be administered in combination with other antihypertensives and/or diuretics and/or angiotensin converting enzyme inhibitors and/or calcium channel blockers. For example, the compounds of this invention can be given in combination with such compounds as amiloride, atenolol, bendroflumethiazide, chlorothalidone, chlorothiazide, clonidine, cryptenamine acetates and cryptenamine tannates, deserpidine, diazoxide, guanethidene sulfate, hydralazine hydroahloride, metolazone, metoprolol tartate, methyclothiazide, methyldopa, methyldopate hydrochloride, minoxidil, pargyline hydrochloride, polythiazide, prazosin, rauwolida serpentina, rescinnaming, sylate, benzithiazide, quinethazone, ticynafan, triamterene, acetazolamide, aminophylline, cyclothiazide, ethacrynic acid, merethoxylline procaine, sodium ethacynate, delapril hydrochloride, enalaprilat, fosinopril sodium, lisinopril, pentopril, quinapril hydrochloride, ramapril, teprotide, zofenopril calcium, diflusinal, diltizem, felodipine, nicardipine, niludipine, minodipine, nisoldipine, nitrenedipine, verapimil and the like, as well as admixtures and combinations thereof. The AII receptor antagonist compounds of this ivnention can also be administered in combination with a monoamine oxidase inhibitor, such as parnate.

To illustrate these combinations, one of the angiotensin II antagonists of

this invention effective clinically in the 2.5-250 milligrams per day range can be effectively combined at levels at the 0.5-250 milligrams per day range with the following compounds at the indicated per day dose range: hydrochlorothiazide (15-200 mg), chlorothiazide (125-2000 mg), ethacrynic acid (15-200 mg), amiloride (5-20 mg), furosemide (5-80 mg), propanolol (20-480 mg) timolol maleate (5-60 mg), methyldopa (65-2000 mg), felodipine (5-60 mg), nifedipine (5-60 mg), and nitrendipine (5-60 mg). In addition triple drug combinations of hydrochlorothiazide (15-200 mg) plus amiloride (5-20 mg) plus angiotnesin II antagonist of this invention (3-200 mg) or hydrochlorothiazide (15-200 mg) plus timolol maleate (5-60 mg) plus an angiotensin II antagonist of this invention (0.5-250 mg) of hydrochlorothiazide (15-200 mg) and nifedipine (5-60 mg) plus an angiotensin II antagonist of this invention (0.5-250 mg) areeffective combinations to control blood pressure in hypertensive patients. Naturally, these dose ranges can be adjusted on a unit basis as necessary to permit divided daily dosage and, the dose will vary depending on the nature and severity of the disease, weight of patient, special diets and other factors.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The method of this invention of antagonizing angiotensin II receptors in mammals, including humans, comprises administering to a subject in need of such antagonism an effective amount of a compound of Formula (I). The method of this invention of producing antihypertensive activity and the method of treating congestive heart failure, glaucoma, and renal failure comprise administering a compound of Formula (I) to a subject in need thereof an effective amount to produce said activity.

Contemplated equivalents of Formula (I) compounds are compounds otherwise corresponding thereto wherein substituents have been added to any of the unsubstituted positions of the Formula (I) compounds provided such compounds have the pharmaceutical utility of Formula (I) compounds.

The following examples illustrate the preparation of compounds and pharmaceutical compositions of this invention. The examples are not intended to limit the scope of this invention as defined hereinabove and as claimed herein-below. The processes detailed in the hereinbefore cited references, which were incorporated by reference, may also be used to prepare the compounds of this invention.

EXAMPLE 1

(E)-3-[2-n-Butyl-1-{[2-(1H-tetrazoly-5-yl)-1,2,3,4-tetrahydronaphthalen-6-yl]methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

A suspension of 2-n-butylimidazol-5-aldehyde (16.92 g, 0.111 mol, U.S. Patent No. 5,185,351), chloromethyl pivalate (21.77 g, 0.145 mol), and potassium carbonate (20.07 g, 0.145 mol) in 200 ml of dimethylformamide was stirred at ambient temperature under argon for four days. The solids were removed by filtration and washed with diethylether. The combined filtrates were partitioned between diethyl ether and water. The ether phase was washed successively with water and brine, dried over magnesium sulfate and concentrated under vaccum to give 23.6 g of 2-n-butyl-1-pivalyloxymethylimidazole-4-aldehyde.

A mixture of 2-cyano-6-iodomethyl-1,2,3,4-tetrahydronaphthalene (0.020 mol, J. Med. Chem., 34:3105 (1991)) and 2-n-butyl-1-pivaloyloxymethyl-imidazole-5-aldehyde (4.45 g, 0.0167 mol) is heated at 100°C under argon for 18 hours. Repeated trituration with ether gives crude product. A suspension of this crude product in 100 ml of ethyl acetate is stirred for 0.5 hours with 100 ml of 5% aqueous sodium carbonate. The layers are separated, the aqueous layer washed with ethyl acetate, and the combined organic layers washed with water, dried over magnesium sulfate and concentrated. Chromatography of the crude extract over silica gel gives 2-n-butyl-1-[(2-cyano-1,2,3,4-tetrahydronaphthalene-6-yl)-methyl]imidazole-5-aldehyde.

Ethyl 2-carboxy-3-(2-thienyl)propionate (14 g, 0.061 mol) was prepared by stirring a solution of diethyl 2-thienylmalonate (16.8 g, 0.0655 mol) and potassium hydroxide (4.41 g, 0.0786 mol) in 200 ml of ethanol under argon at room temperature for 12 days and then purifying by removing the solvent under vacuum, dissolving the reside in water, washing the aqueous layer with aqueous hydrochloric acid and with diethyl ether.

A solution of this half-acid, half-ester (1.05 g, 4.62 mmol) in 5 ml of toluene is added to a refluxing solution of 2-n-butyl-1-[(2-cyano-1,2,3,4-tetrahydronaphthalene-6-yl)methyl]imidazole-5-aldehyde (3.08 mmol) and piperidine (0.26 g, 3.08 mmol) in 60 ml of toluene. Twice, at 1 hour intervals, an additional 1 g of the half-acid, half-ester is added, and the solution is then refluxed for 17 hours. Evaporation of the toluene and chromatography of the residue over silica gel gives ethyl (E)-3-[2-n-butyl-1-{2-cyano-1,2,3,4-tetrahydronaphthalene-6-yl]methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate.

Tetrahydrofuran (8 ml) is added slowly under argon with stirring to a mixture of ethyl (E)-3-[2-n-butyl-1-{2-cyano-1,2,3,4-tetrahydronaphthalene-6-

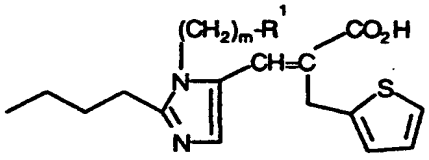
yl]methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate (2.15 mmol) and aluminum chloride (4.33 mmol). Sodium azide (1.28 g, 19.43 mmol) is added all at once, followed by a 1 ml tetrahydrofuran rinse, and the reaction is heated to 65°C for 22 hours, then cooled to room temperature. The reaction mixture is diluted with ethyl acetate (8 ml) and treated with 10% hydrochloric acid solution (8 ml) with vigorous stirring for 5 minutes. The ethyl acetate layer is washed with water and brine. The combined aqueous layers are extracted once with ethyl acetate. The ethyl acetate layers are combined, dried with anhydrous sodium sulfate and evaporated to give ethyl (E)-3-[2-n-butyl-1-{[2-(1H-tetrazoly-5-yl)-1,2,3,4-tetrahydronaphthalen-6-yl]methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate.

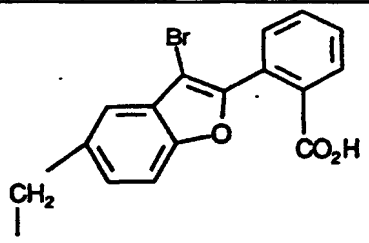
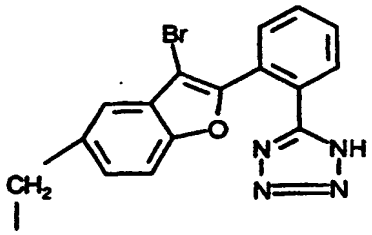
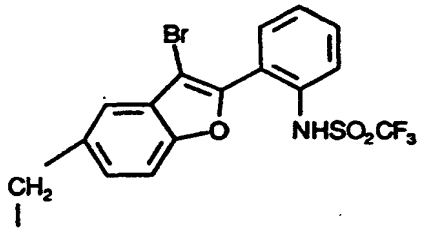
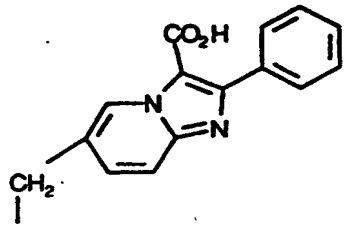
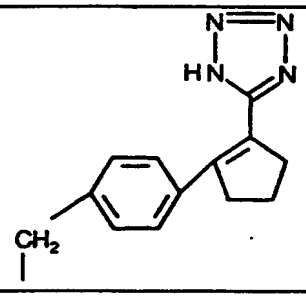
A solution of ethyl (E)-3-[2-n-butyl-1-{[2-(1H-tetrazoly-5-yl)-1,2,3,4-tetrahydronaphthalen-6-yl]methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate. (0.783 mmol) in ethanol (10 ml) is treated with 10% sodium hydroxide solution (4 ml), and the solution is stirred for 3 hours at 25°C. The pH is adjusted to 5 and a solid precipitated. The mixture is diluted with water, cooled and filtered to provide the title compound.

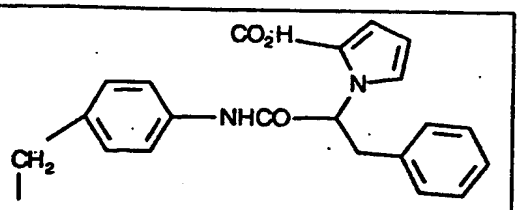
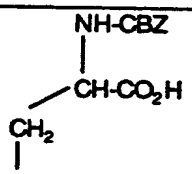
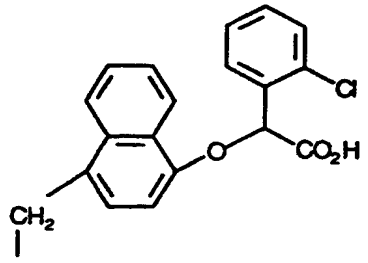
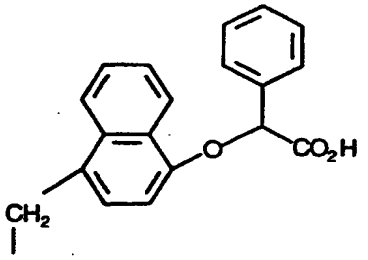
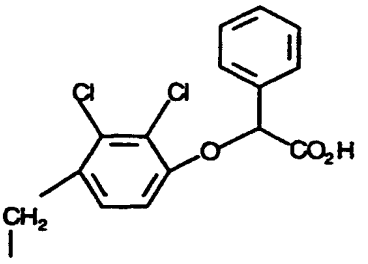
EXAMPLES 2-13

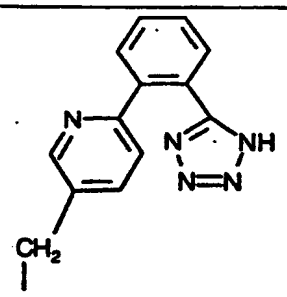
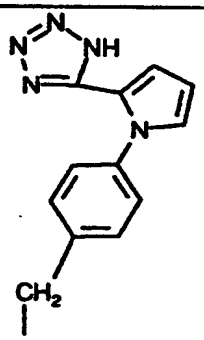
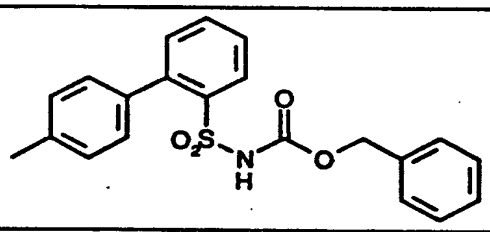
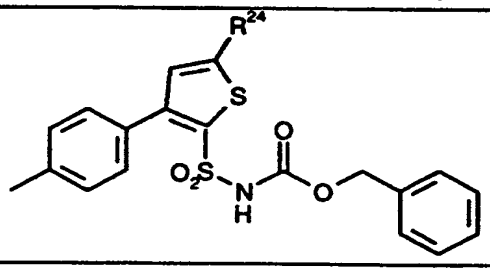
Examples 2-13 in Table I are prepared following the procedure of Example 1 using the appropriate $R^1(CH_2)_m$-bromide or -iodide group in place of 2-cyano-6-iodomethyl-1,2,3,4-tetrahydronaphthalene. (See the specification on pages 18-19 for the preparation of the R^1-$(CH_2)_m$-bromides or -iodides.)

TABLE I



Example	$-(CH_2)_m-R^1$ Group
2	
3	
4	
5	
6	

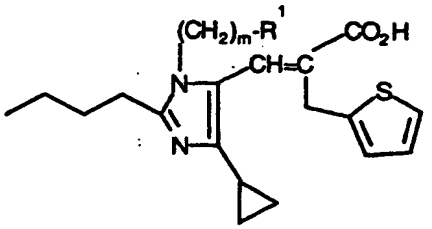
7	
8	
9	
10	
11	

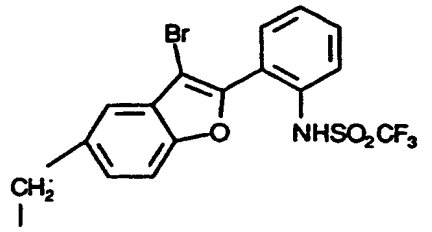
12	
13	
14	
15	

EXAMPLE 16

Example 16 in Table II is prepared following the procedure of Example 1.

TABLE II



Example	$-(CH_2)_m-R^1$ Group
16	

EXAMPLE 17

An oral dosage form for administering orally active Formula (I) compounds is produced by screening, mixing and filling into hard gelatin capsules the ingredients in proportions, for example, as shown below.

Ingredients	Amounts
(E)-3-[2-n-butyl-1-{(3-bromo-2-[2-(tetrazol-5-yl)phenyl]benzofuran-4-yl]methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid	100 mg
magnesium stearate	10 mg
lactose	100 mg

EXAMPLE 18

The sucrose calcium sulfate dihydrate and orally active Formula (I) compounds are mixed and granulated with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, screened

and compressed into a tablet.

Ingredients	Amounts
(E)-3-[2-n-butyl-1-{(3-bromo-2-[2-(tetrazol-5-yl)phenyl]benzofuran-4-yl]methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid	75 mg
calcium sulfate dihydrate	100 mg
sucrose	15 mg
starch	8 mg
talc	4 mg
stearic acid	2 mg

EXAMPLE 19

(E)-3-[2-n-Butyl-1-{[2-(1H-tetrazoly-5-yl)-1,2,3,4-tetrahydronaphthalen-6-yl]methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, 50 mg, is dispersed in 25 mL of normal saline to prepare an injectable preparation.

EXAMPLE 20

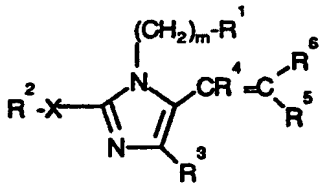
A topical opthamological solution for administering Formula (I) compounds is produced by mixing under sterile conditions the ingredients in proportions, for example, as shown below.

Ingredients	Amounts (mg/mL)
(E)-3-[2-n-butyl-1-{[2-(1H-tetrazoly-5-yl)-1,2,3,4-tetrahydronaphthalen-6-yl]methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid	1.0
dibasic sodium phosphate	10.4
monobasic sodium phosphate	2.4
chlorobutanol	5.0
hydroxypropanol methylcellulose	5.0
sterile water	q.s.ad 1.0mL
1.0 N sodium hydroxide	q.s.ad pH 7.4

It is to be understood that the invention is not limited to the embodiments illustrated hereinabove and the right to the illustrated embodiments and all modifications coming within the scope of the following claims is reserved.

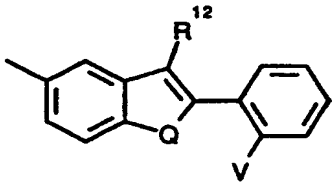
What is claimed is:

1. A compound of the formula:

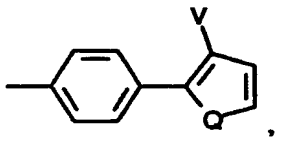


in which:

R^1 is



(1)



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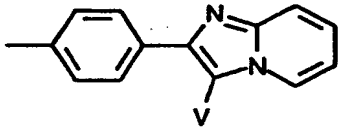
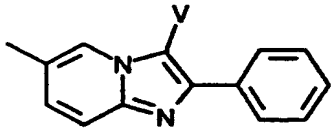


(3)



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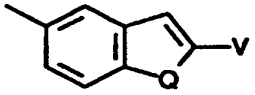

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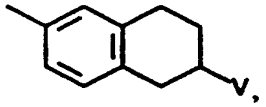

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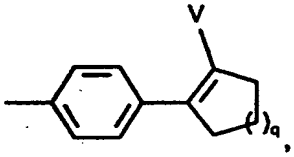

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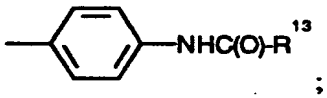

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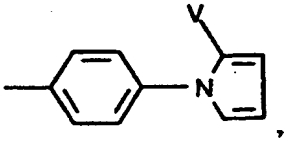

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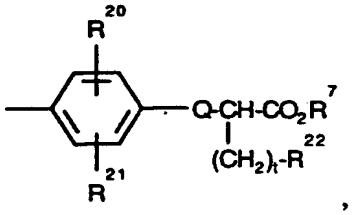

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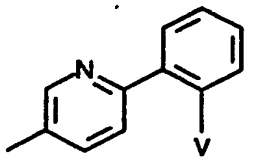

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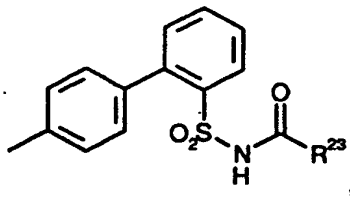

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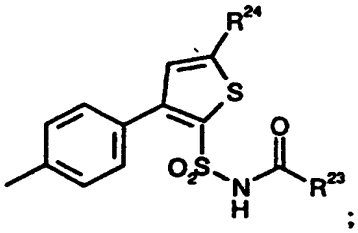
, or



(13)

;

m is 0-4;

R^2 is C_2-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl, $(CH_2)_{0-8}$-C_3-C_6cycloalkyl, or $(CH_2)_{0-8}$phenyl unsubstituted or substituted by one to three substituents selected from C_1-C_6alkyl, nitro, Cl, Br, F, I, hydroxy, C_1-C_6alkoxy, NR^7R^7, CO_2R^7, CN, $CONR^7R^7$, W, tetrazol-5-yl, NR^7COC_1-C_6alkyl, NR^7COW, SC_1-C_6alkyl, SO_2W, or SO_2C_1-C_6alkyl;

X is a single bond, S, NR^7, or O;

R^3 is hydrogen, Cl, Br, F, I, CHO, hydroxymethyl, $COOR^7$, $CONR^7R^7$, NO_2, W, CN, NR^7R^7, phenyl, C_1-C_6alkyl, or $(CH_2)_{0-4}$-C_3-C_6cycloalkyl;

R^4 and R^5 independently are hydrogen, C_1-C_6alkyl, phenyl-Y-, biphenyl-Y-, naphthyl-Y-, 2- or 3-thienyl-Y-, 2- or 3-furanyl-Y-, 2-, 3- or 4-pyridyl-Y-, pyrazolyl-Y-, imidazolyl-Y-, pyrrolyl-Y-, triazolyl-Y-, oxazolyl-Y-, isoxazolyl-Y-, thiazolyl-Y-, or tetrazolyl-Y-, except that R^4 and R^5 are not selected from hydrogen and C_{1-6}alkyl, and with each heteroaryl group being unsubstituted or substituted by C_1-C_6alkyl, C_1-C_6alkoxy, Cl, Br, F, I, CF_3, NR^7R^7, CO_2R^7, SO_2NHR^7, SO_3H, $CONR^7R^7$, OH, NO_2, SC_1-C_6alkyl, SO_2C_1-C_6alkyl, NR^7COH, or NR^7COC_1-C_6alkyl and with each aryl group being unsubstituted or substituted by one to three substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, Cl, Br, F, I, CF_3, NR^7R^7, CO_2R^7, SO_2NHR^7, SO_3H, $CONR^7R^7$, OH, NO_2, SC_1-C_6alkyl, SO_2C_1-C_6alkyl, NR^7COH, or NR^7COC_1-C_6alkyl or with each aryl group being substituted by methylenedioxy, phenoxy, or phenyl;

Y is a single bond, O, S, or C_1-C_6alkyl which is straight or branched or

optionally substituted by phenyl or benzyl, wherein each of the aryl groups is unsubstituted or substituted by halo, NO_2, CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, CN, or CO_2R^7;

R^6 is -Z-$COOR^8$ or -Z-$CONR^7R^7$;

Z is a single bond, vinyl, -CH_2-O-CH_2-, methylene optionally substituted by C_1-C_6alkyl, one or two benzyl groups, thienylmethyl, or furylmethyl, or -C(O)$NHCHR^9$-, wherein R^9 is H, C_1-C_6alkyl, phenyl, benzyl, thienylmethyl, or furylmethyl;

W is C_nF_{2n+1};

each R^7 independently is hydrogen, C_1-C_6alkyl, or $(CH_2)_p$phenyl;

each n independently is 1-3;

each p independently is 0-4;

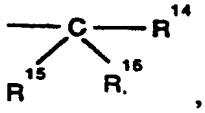
R^8 is hydrogen, C_1-C_6alkyl, or 2-di(C_1-C_6alkyl)-amino-2-oxoethyl;

each R^{10} independently is H or C_1-C_6alkyl;

R^{11} is H, C_{1-6}alkyl, C_nF_{2n+1}, or -$(CH)_{0-2}$phenyl which is unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I, C_1-C_6alkyl, NO_2, CF_3, CO_2R^{10}, tetrazolyl, C_1-C_6alkoxy, OH, SC_1-C_6alkyl, SO_2NHR^{10}, $NHSO_2R^{10}$, SO_3H, $CONR^{10}R^{10}$, CN, SO_2C_1-C_6alkyl, $NR^{10}R^{10}$, $NR^{10}COH$, $NR^{10}COC_1$-C_6alkyl, or $NR^{10}CO$-phenyl;

R^{12} is H, Br, Cl, F, I, CF_3, C_{1-4}alkyl, or C_1-C_4alkoxy;

R^{13} is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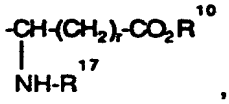
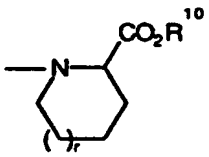

,

-$CH(R^{18})$-NHR^{17},

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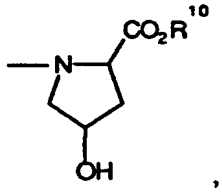
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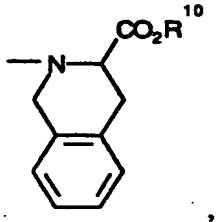
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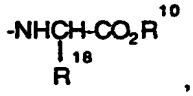
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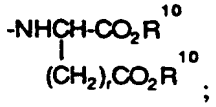
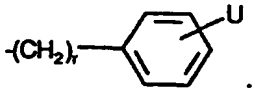
or

;

R^{14} is H, C_1-C_4alkyl, or

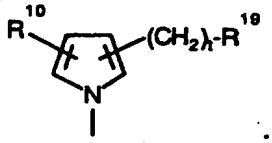


;

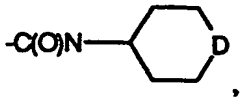
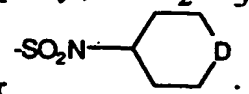
U is absent or present as Cl, Br, F, I, C_1-C_6alkyl, C_1-C_6alkoxy, or hydroxy;

R^{15} is hydrogen;

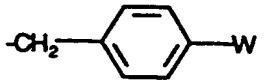
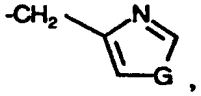
R^{16} is CN, CO_2H, tetrazolyl, or



;

each R^{17} is CBZ, BOC, CO-phenyl, $COCH_2CH_3$, $COCH_3$, $COCF_3$, $CONR^{10}R^{10}$,  , or  ;

R^{18} is H, C_{1-6}alkyl,

 ,  ,

$-(CH_2)_3-NHC(=N)NH_2$, or $-(CH_2)_{3-4}NH_2$;

R^{19} is H, C_1-C_6alkyl, phenyl, CN, COR^{10}, CO_2R^{10}, tetrazolyl or

 ;

R^{20} and R^{21} independently are H, C_1-C_6alkyl, Cl, Br, F, I, C_1-C_6alkoxy, or phenyl, or when R^{20} and R^{21} are on adjacent carbon atoms, they are joined to form a phenyl ring;

R^{22} is $(CH_2)_{0-2}$phenyl unsubstituted or substituted by one to five substituents selected from Cl, Br, I, F, C_1-C_6alkyl, C_{1-5}alkoxy, C_{1-5}alkylthio, NO_2, CF_3, CO_2R^7, or OH;

each R^{23} independently is $-OCH_2$-phenyl unsubstituted or substituted by NHR^{25} or OR^{26};

R^{24} is C_1-C_4alkyl or C_3-C_6cycloalkyl;

R^{25} is H, C_1-C_4alkyl, C_3-C_6cycloalkyl or phenyl;

R^{26} is C_1-C_4alkyl or C_3-C_6cycloalkyl;

each Q independently is -O-, -S-, or $-N(R^{10})-$;

V is CO_2R^{10}, tetrazolyl, or $-NHSO_2R^{11}$;

q is 1-3;
each r independently is 0-3;
each t independently is 0-2;
A is CH or N;
D is $-CH_2-$, -O-, or $-N(R^{10})-$;
W is absent or present as OH or OC_{1-6}alkyl; and
G is -O-, -S-, or -NH-;
or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 in which one of R^4 and R^5 is hydrogen or C_1-C_4alkyl and m is one.

3. The compound of claim 2 in which X is a single bond and R^2 is C_2-C_8alkyl.

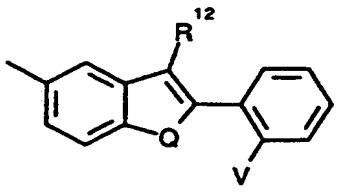
4. The compound of claim 3 in which R^3 is hydrogen, chloro, fluoro, trifluoromethyl, C_1-C_6alkyl, or C_3-C_6cycloalkyl and R^4 is hydrogen or C_1-C_4alkyl.

5. A compound of claim 4 in which R^6 is COOH, $COOC_{1-2}$alkyl or $CONH_2$.

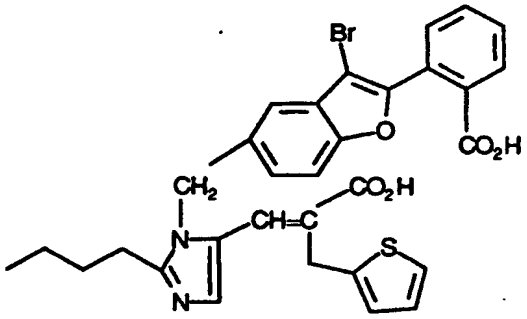
6. The compound of claim 5 in which R^5 is thienylmethyl, furylmethyl, or imidazolylmethyl, each of which is optionally substituted by methyl or methoxy.

7. The compound of claim 8 which is the E isomer, wherein the R^6 group and the imidazole are trans to each other.

8. The compound of claim 7 in which R^1 is

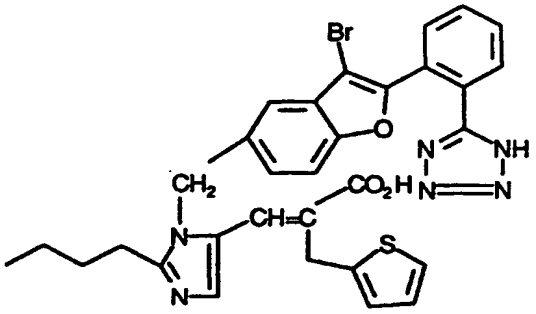


9. The compound of claim 8 which is



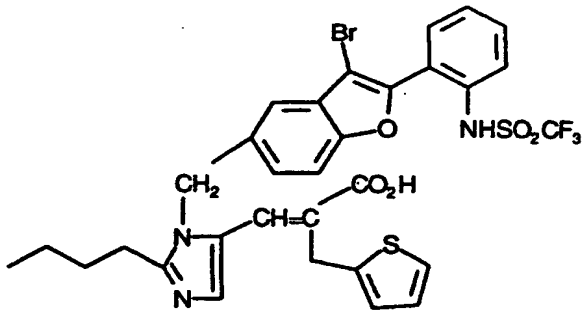
or a pharmaceutically acceptable salt thereof.

10. The compound claim 8 which is



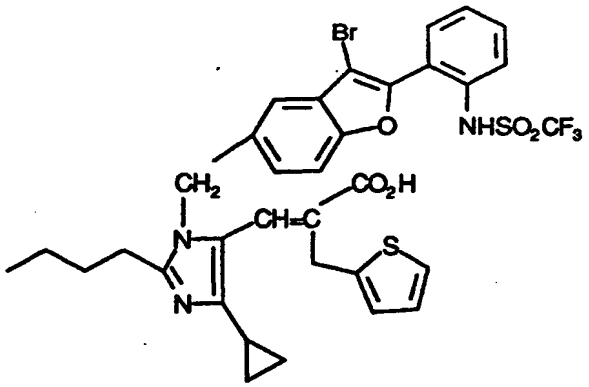
or a pharmaceutically acceptable salt thereof.

11. The compound of claim 8 which is



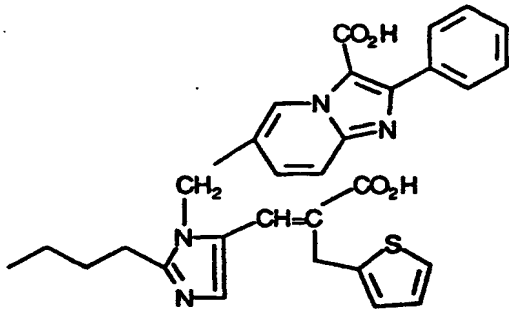
or a pharmaceutically acceptable salt thereof.

12. The compound of claim 8 which is



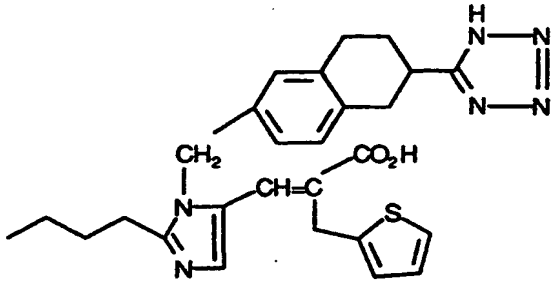
or a pharmaceutically acceptable salt thereof.

13. The compound of claim 7 which is



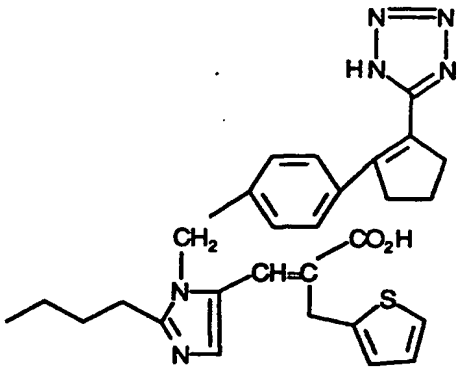
or a pharmaceutically acceptable salt thereof.

14. The compound of claim 7 which is



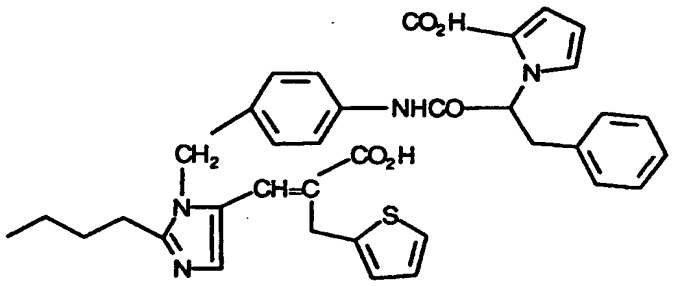
or a pharmaceutically acceptable salt thereof.

15. The compound of claim 7 which is



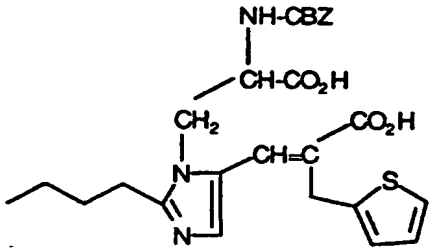
or a pharmaceutically acceptable salt thereof.

16. The compound of claim 7 which is



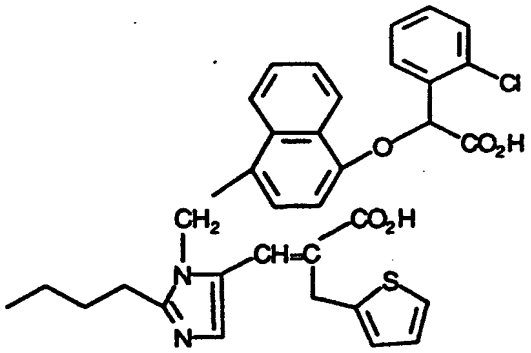
or a pharmaceutically acceptable salt thereof.

17. The compound of claim 7 which is



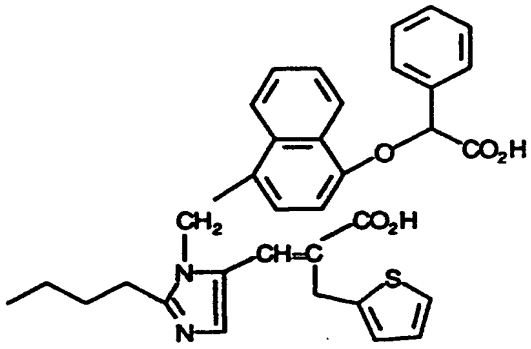
or a pharmaceutically acceptable salt thereof.

18. The compound of claim 7 which is



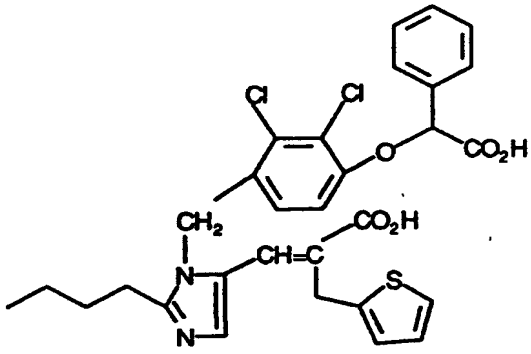
or a pharmaceutically acceptable salt thereof.

19. The compound of claim 7 which is



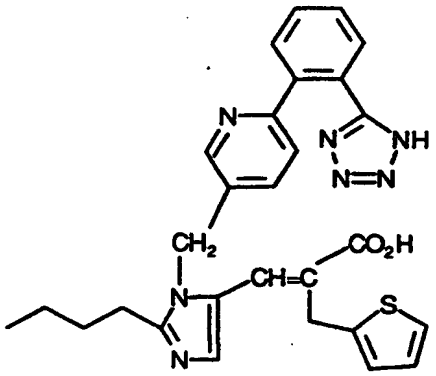
or a pharmaceutically acceptable salt thereof.

20. The compound of claim 7 which is



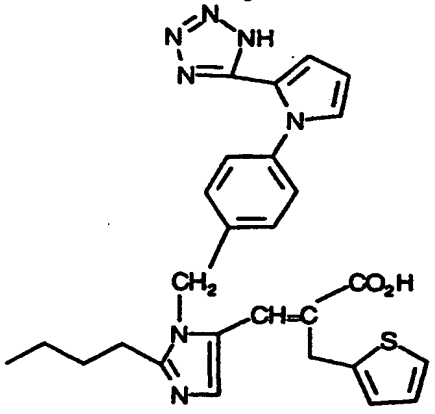
or a pharmaceutically acceptable salt thereof.

21. The compound of claim 7 which is



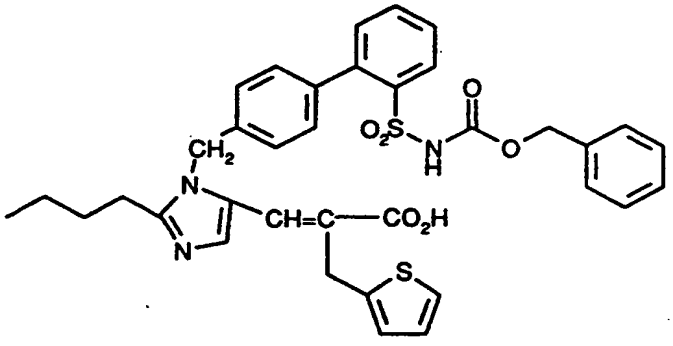
or a pharmaceutically acceptable salt thereof.

22. The compound of claim 7 which is



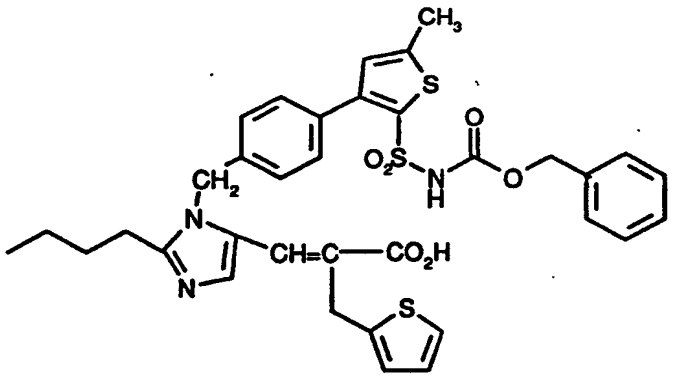
or a pharmaceutically acceptable salt thereof.

23. The compound of claim 7 which is



or a pharmaceutically acceptable salt thereof.

24. The compound of claim 7 which is



or a pharmaceutically acceptable salt thereof.

25. A pharmaceutical composition comprising a pharmaceutical carrier and a compound of claim 1.

26. A method of antagonizing angiotensin II receptors which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

27. A method of treating hypertension which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

28. A method of treating congestive heart failure which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

29. A method of treating renal failure which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

30. A method of treating glaucoma which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/05762

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/300, 381, 382, 397 ; 546/121, 276 ; 548/253, 311.4, 314.7, 315.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A, 5,212,198 (DJURIC et al) 18 MAY 1993, see entire document.	1-30
A	US,A, 5,145,858 (ADAMS et al) 08 SEPTEMBER 1992, see entire document.	1-30
A	US, A, 5,073,566 (LIFER et al) 17 DECEMBER 1991, see entire document.	1-30

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 SEPTEMBER 1994	SEP 19 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer DAVID B. SPRINGER Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/05762

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (5):

A61K 31/41, 31/415, 31/435, 31/44 ; C07D 401/14, 403/14, 405/14, 409/06, 409/14

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/300, 381, 382, 397 ; 546/121, 276 ; 548/253, 311.4, 314.7, 315.1